

## REMARKS

Claims 1, 4, 5, 8-23 and 26-32 were pending prior to this Response. By the present communication, no claims have been added or canceled, and claims 1 and 32 have been amended to correct typographical errors. Applicant respectfully requests entry of the amendments set forth in this response under 37 CFR §1.116. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, claims 1, 4, 5, 8-23 and 26-32 are currently pending in this application.

### **Information Disclosure Statement**

The Information Disclosure Statement (IDS) has been objected to as allegedly being improper by not listing all patents, publications or other information submitted for consideration by the Office. Specifically, one of the references cited in the IDS appears to have a typographical error. Attached herewith is a corrected IDS Form 1449 listing the correct spelling of Sommers, et al. for consideration by the Office.

### **Rejection of under 35 U.S.C. §103**

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8, 19-27 and 29-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers et al. (hereinafter "Sommers") in view of Herrick-Davis et al. (hereinafter "Herrick-Davis"). The burden of proof in establishing a *prima facie* case of obviousness under §103 clearly rests with the Patent Office. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the

manner claimed.” *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must “explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination.” *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). “The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.” *In re Sang Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (citations omitted).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to combine and modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the various references and stated that the combination of these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that “[b]road conclusory statements regarding the teaching of multiple references standing alone are not ‘evidence’.” *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. “Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority.” *In re Sang Su Lee* 277 F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The Examiner relies upon Sommers for disclosure of random as well as site directed mutagenesis to substitute the amino terminus and transmembrane regions of the STE2 gene in yeast. Specifically, Sommers discloses deleting the endogenous STE2 gene and providing external STE genes encoding several mutants of  $\alpha$ -factor receptor to study the effects of various antagonists and agonists and to find out the amino acids responsible for switching a receptor between active and inactive stages. However, Sommers does not teach providing a library of coding sequences for potentially activating mutations of a candidate receptor or ion channel, which library is generated by

replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Sommers discloses screening a library of *random* mutations to the amino terminus and transmembrane regions of the STE2 gene in yeast. Then, “[m]utations identified by screening of the PCR-generated libraries *were recreated* by site-directed mutagenesis to separate the multiple substitutions that were present in most alleles and to confirm that the identified sequence alterations were responsible for the altered phenotype.” (Sommers, p. 6901, col. 2, first paragraph, emphasis added). Accordingly, the mutations of Sommers are initially identified and selected from a random library, while the mutations of the current invention are identified directly from a library of site directed mutations.

Furthermore, approximately half of the isolated mutants identified by Sommers substitute in amino acids that fall within the definition of “small side-chain amino acids,” as provided by Applicant’s specification (see page 17 of the specification as filed). Accordingly, Sommers is silent with regard to providing a library of coding sequences, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention.

The disclosure of Herrick-Davis does not cure the above-described deficiencies in Sommers for teaching or suggesting the claimed invention. Herrick-Davis allegedly discloses application of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. Specifically, Herrick-Davis discloses that mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT<sub>2c</sub> receptor activates the receptor. The library is expressed in a mammalian host cell. However, according to the Examiner, Herrick-Davis does “not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene.” (Office Action dated December 15, 2004, page 8). Further, Herrick-Davis specifically states that “the increases in agonist binding affinity and potency at the mutant receptors did not result from increased receptor expression but are *directly related to the substitutions made at amino acid no.*

312.” (Herrick-Davis, page 1141, col. 1, lines 1-5, emphasis added). Further, “[a]dditional studies were performed to determine if agonists other than 5-HT display an increased affinity for S312K receptors.” (Herrick-Davis, page 1140, col. 2, first paragraph). Herrick-Davis does not disclose, nor even suggest substitution of amino acids other than no. 312.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it prima facie obvious to combine the disclosures of Sommers and Herrick-Davis to arrive at Applicants’ invention. Even if one were motivated to combine Sommers with Herrick-Davis, Applicants submit that the proposed combination would teach away from creating a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids because (1) Sommers’ library consists of random mutations; (2) Sommers’ substitutions are not limited to those required by Applicants’ invention; (3) Herrick-Davis does not disclose or suggest the library of coding sequences as required by Applicants’ invention; and (4) Herrick-Davis focuses solely on amino acid no. 312 of the receptor. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 9-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers in view of Herrick-Davis and further in view of Barak, et al. (hereinafter “Barak”). The remarks above distinguishing the invention over the disclosures of Sommers and Herrick-Davis apply equally here. Barak allegedly discloses using a heterologous reporter system where the reporter gene green fluorescent protein is made in fusion with beta arrestin under mammalian promoter control, and is expressed in cells such as insect cells, plant or animal cells including, but not limited to, HEK cells, HeLa cells, COS cells and primary cells. However, Barak is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Barak with Sommers and Herrick-Davis to arrive at the claimed invention. Even if one were motivated to combine Barak with Sommers and Herrick-Davis, Applicants submit that the

proposed combination would not yield the claimed invention because Barak is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers in view of Herrick-Davis and Barak, further in view of Lerner, et al. (hereinafter "Lerner"). The remarks above distinguishing the invention over the disclosures of Sommers, Herrick-Davis and Barak apply equally here. Lerner allegedly discloses identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. However, Lerner is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Lerner with Sommers, Herrick-Davis and Barak to arrive at the claimed invention. Even if one were motivated to combine Lerner with Sommers, Herrick-Davis and Barak, Applicants submit that the proposed combination would not yield the claimed invention because Lerner is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8, 10, 19-24, 26 and 29-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat, et al. (hereinafter "Dahiyat"). As discussed above, Herrick-Davis discloses that mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT<sub>2c</sub> receptor activates the receptor. The library is expressed in a mammalian host cell. However, according to the Examiner, Herrick-Davis does "not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene." (Office Action dated December 15, 2004, page 8). Further, Herrick-

Davis specifically states that “the increases in agonist binding affinity and potency at the mutant receptors did not result from increased receptor expression but are *directly related to the substitutions made at amino acid no. 312.*” (Herrick-Davis, page 1141, col. 1, lines 1-5, emphasis added). Further, “[a]dditional studies were performed to determine if agonists other than 5-HT display an increased affinity for S312K receptors.” (Herrick-Davis, page 1140, col. 2, first paragraph). Herrick-Davis does not disclose, nor even suggest substitution of amino acids other than no. 312.

The disclosure of Dahiyat does not cure the above-described deficiencies in Herrick-Davis for teaching or suggesting the claimed invention. Dahiyat allegedly discloses a method of designing a protein library for the substitution of residues in any part of a protein, and that a protein sequence can be designed through a fully automated sequence selection process to accomplish a library of a protein having various changes in the amino acids. While Dahiyat discloses that the automated sequence selection is an unbiased way of selecting amino acids for protein structure and function, and that it is not limited to a particular motif or folding sequences, Dahiyat does not limit the mutations to replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Dahiyat with Herrick-Davis to arrive at the claimed invention. Even if one were motivated to combine Dahiyat with Herrick-Davis, Applicants submit that the proposed combination would not yield the claimed invention because Dahiyat is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat and King, and further in view of Lerner. Applicants respectfully submit that the remarks above with regard to the differences between Herrick-Davis in view of Dahiyat apply equally here. The Examiner relies upon King for disclosing that reconstruction of a heterologous reporter system using the  $\beta$ -galactosidase gene (lacZ) in yeast would elucidate understanding of a ligand binding to the G protein coupled receptor and its activation. However, King does not disclose providing a library of coding sequences for

potentially activating mutations of a candidate receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. King further does not disclose expression of a library of mutant alleles in mammalian host cells to determine activation of a receptor by the mutants.

As discussed above, Lerner is concerned with identifying new drugs through expression in pigment cells. Lerner is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Lerner with Herrick-Davis, Dahiyat and King to arrive at the claimed invention. Even if one were motivated to combine Lerner with Herrick-Davis, Dahiyat and King, Applicants submit that the proposed combination would not yield the claimed invention because both Lerner and King are absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that *prima facie* obviousness of the invention over the cited references, either alone or in combination, has not been shown by the Examiner. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 for alleged lack of patentability are respectfully requested.

Applicants: Beachy and Taipale  
Application No.: 09/943,641  
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In summary, for the reasons set forth herein, Applicants maintain that claims 1, 4, 5, 8-23 and 26-32 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Applicants submit a check number 579858 in the amount of \$475.00 for the Notice of Appeal fee and the two-month extension of time fee. No other fee is deemed necessary in connection of the filing of this document. However, the Commissioner is hereby authorized to charge for any additional required fees, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

A handwritten signature in cursive script, reading "Lisa A. Haile", written in black ink over a horizontal line.

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